A Genetic Study of Dehydroepiandrosterone Sulfate Measured Before and After a 20-Week Endurance Exercise Training Program: The HERITAGE Family Study

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Familial aggregation and possible major gene effects were evaluated for the baseline serum dehydroepiandrosterone sulfate (DHEAS) level and the change in DHEAS in response to a 20-week exercise training program in a sample of 481 individuals from 99 Caucasian families who were sedentary at baseline and who participated in the HERITAGE Family Study. Baseline DHEAS levels were not normally distributed, and were therefore logarithmically transformed and adjusted for the effects of age and sex prior to genetic analysis. The DHEAS response to training was computed as the simple difference, post-training minus baseline, and was adjusted for the baseline DHEAS level, age, and sex. Maximal (genetic and familial environmental) heritabilities (using a familial correlation model) reached 58% and 30% for the baseline and the response to training, respectively. Our estimate for the baseline is generally in agreement with previous reports, suggesting that the magnitude of the familial effect underlying this phenotype in these sedentary families is similar to that in the general population. However, segregation analysis showed no evidence for a multifactorial familial component in data for either the baseline or the response to training. Rather, a major additive gene controlling the baseline was found. For the response to training in the complete sample, transmission of the major effect from parents to offspring was ambiguous, but in a subset of 56 "responsive" families (with at least 1 family member whose response to training was greater than 1 standard deviation) this major effect was Mendelian in nature. The putative major genes accounted for 50% and 33% of the variance for the baseline and the response to training, respectively. The novel finding in this study is that the baseline DHEAS level and the change in DHEAS in response to training may be influenced by major gene effects.

DEHYDROEPIANDROSTERONE SULFATE (DHEAS) is a major circulating form of dehydroepiandrosterone (DHEA) and a metabolic precursor of testosterone and estradiol. Blood concentrations of DHEAS are higher than any other adrenal steroid levels in both men and women. It has been suggested that DHEAS levels may be inversely associated with an increased risk for cardiovascular disease,[1] obesity, and diabetes mellitus.[2-3] DHEAS is reported to be associated with many other cardiovascular disease risk factors,[4] and an increase of DHEAS appears to provide protective effects against these diseases.[4] Levels of DHEAS vary markedly with age. They are very low in childhood, increase rapidly with the onset of puberty (about age 15), with the highest levels in the third decade of life (about age 25 to 30), and then decrease progressively with advancing age.[5-6] There are also recognized age-related sex differences in DHEAS levels, with higher levels in males versus females after puberty.[2,7-8]

A familial component for DHEAS was demonstrated previously in a twin study[9] and three family studies.[7-8,10] The reported magnitude of the effect varies considerably from 39%[8] to 65%.[10] Furthermore, Rice et al[7] also suggested that the heritability varied by sex (29% in males and 74% in females). No commingling or segregation analyses of DHEAS have been reported previously. Thus, the current study explores for the first time whether there is a major gene effect on DHEAS levels either at baseline or in response to exercise training.

A single exercise session acutely increases DHEAS.[2] According to Velardo et al,[11] DHEAS increased significantly in response to 1 hour of swimming. It is controversial as to whether regular exercise has any chronic effect on DHEAS concentrations.[2] Two studies suggested that DHEAS increased after exercise training,[12-13] while Milani et al[14] questioned whether exercise therapy alone could affect DHEAS levels. No previous studies have explored a familial basis for changes in DHEAS levels in response to training.

The initial physical activity level was controlled for in the HERITAGE Family Study by requiring all participants to be sedentary at baseline, ie, not engaging in regular physical activity over the previous 6 months. This study is unique in that DHEAS levels were assessed prior to and following a 20-week endurance exercise training program in intact families, and thus familial aggregation and a major gene hypothesis for both data for the baseline and the response to training can be assessed.

SUBJECTS AND METHODS

Sample

The HERITAGE Family Study was designed to investigate the role of the genotype in cardiovascular, metabolic, and hormonal responses to aerobic exercise training and the contribution of regular exercise to changes in cardiovascular disease and diabetes risk factors. See Bouchard et al[15] for more details concerning the HERITAGE Family Study sample and protocol.

A total of 481 individuals in 99 families (including one 3-generation family that was then divided into two nuclear families) of Caucasian descent (233 males and 248 females) completed the training protocol. Participants with incomplete baseline or post–exercise training DHEAS measurements were excluded from the analysis for the response to training. A total of 477 individuals were eligible for analysis of the DHEAS response to training. If the DHEAS response to training is influenced by major gene(s), then a variation in the responsiveness to

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training in individuals within families should be expected. The DHEAS response to training was thus further analyzed separately in a subset of 56 "responsive" families (301 individuals), defined in the current study as having at least one family member whose DHEAS response to training (increasing or decreasing) exceeded 1 standard deviation (SD). Data from one individual (a father) with an extreme DHEAS response to training (15 SD from the mean) were not included in the current analysis. Table 1 lists the sample sizes within each of 4 sex × generation groups (fathers, mothers, sons, and daughters) for baseline DHEAS and the DHEAS response to training, respectively. Families of African-American descent also were recruited and tested in the HERITAGE Family Study, but their results are not reported here. The study protocol was approved by the Institutional Review Board at each participating clinical center. Recruitment of families was based on extensive media publicity and advertisements at the 4 participating clinical centers.

The following entry criteria were applied to screen subjects for participation. First, individuals had to be between the ages of 17 and 65 years (17 to 40 years for children and ≤65 years for parents). Second, all participants were required to be sedentary at baseline. Third, a body mass index (BMI) less than 40 kg/m^2 was required unless a physician certified that the subject was able to meet the demands of the exercise tests and exercise training program. Fourth, resting blood pressure (BP) was 159 mm Hg or less for systolic BP and 99 mm Hg or less for diastolic BP in the absence of medication. Finally, participants were required to be in good general physical health to complete the 20-week exercise training program. Exclusion criteria can be found in Bouchard et al.[15]

Exercise Training Program

The training protocol is thoroughly discussed in Bouchard et al.[15] Briefly, each individual trained on a cycle ergometer in the laboratory under supervision 3 times per week for 20 weeks. Participants exercised for 30 minutes at the heart rate associated with 55% of their maximal oxygen intake during the first 2 weeks. The intensity or duration of exercise was adjusted every 2 weeks thereafter so that participants were working for 50 minutes at the heart rate associated with 75% of their maximum during the last 6 weeks of training. The power output was adjusted automatically by computer so that the desired training heart rate was maintained. All training sessions were supervised on site, and adherence to the protocol was strictly monitored.

Table 1. Baseline DHEAS and DHEAS Response to Training (nmol/L)

Variable	Fathers			Mothers		
	No.	Mean	SD	No.	Mean	SD
Age (yr)†	94	53.4	5.5	90	52.1	5.1
BMI (kg/m^2)†	94	28.3	4.5	90	27.5	4.8
Baseline						
DHEAS†	94	3,627*	2154	90	2,345*	1,452
Log DHEAS†	94	8.0*	0.6	90	7.6*	0.7
Response to training						
DHEAS‡	93	89	702	90	0	655
DHEAS§	59	171	764	55	−1	767
	Sons			Daughters		
Age (yr)†	139	25.5	6.1	158	25.6	6.5
BMI (kg/m^2)†	138	25.7*	4.9	158	23.5*	4.3
Baseline						
DHEAS†	139	7,477*	3,331	158	4,551*	2,281
Log DHEAS†	139	8.8*	0.5	158	8.3*	0.5
Response to training						
DHEAS	139	−45	1,600	155	−86	1,357
DHEAS	94	−26	1,902	93	−109	1,696

*Significant ($P < .05$) mean differences for father-mother or son-daughter (within-generation) comparisons.

†Significant ($P < .05$) mean differences for father-son or mother-daughter (within-sex) comparisons.

‡The response to training in the complete sample.

§The response to training in the subset of 56 responsive families.

Measurements

Before and after the 20-week standardized exercise training program, blood samples from an antecubital vein were obtained in vacutainer tubes containing EDTA, from which serum DHEAS concentrations were measured. The blood samples were collected in the morning after a 12-hour fast with the participants in a semirecumbent position, and were obtained twice before training (24 hours apart) and twice near the end of training (at least 24 hours apart and at least 20 hours after a training session). The blood samples collected at each clinical center were prepared according to a standard protocol before shipment to the core laboratory in Quebec, and were adjusted for possible post-training hemodilution by protein assays. Serum DHEAS concentrations were determined by a specific radioimmunoassay using Diagnostic Products (San Antonio, TX) kits. The sensitivity of the assay is high, and it can detect as little as 1.1 μg/dL. In addition, the antiserum also is highly specific to DHEAS, with very low cross-reactivity with other blood compounds. No effects of bilirubin and hemolysis on the assay were found to be significant.

Data Adjustments

Baseline DHEAS was adjusted for the effects of age within each of the 4 sex × generation groups using a stepwise multiple regression procedure. Briefly, a given measurement was regressed on a polynomial in age (linear, quadratic, and cubic) in a stepwise manner retaining only terms that were significant at the 5% level. Thus, the residual score from this regression is independent of age, sex, and generation effects. A similar set of stepwise regressions (by sex and generation groups) were also performed by regressing baseline DHEAS on a polynomial in age (age, age^2 and age^3) and BMI (linear). The DHEAS response to training was adjusted for the effects of the polynomial in age and baseline DHEAS (linear) within each of the 4 sex × generation groups. Each of the final adjusted phenotypes used in the genetic analysis was standardized to a mean of zero and a SD of 1.

Familial Correlation Model

A sex-specific familial correlation model was used to investigate whether there is evidence of familial effects underlying the variation in either the adjusted baseline DHEAS or the DHEAS response to training. The computer program SEGPATH[16] was used to fit the model directly to the family data using the method of maximum likelihood under the assumption that the phenotypes within a family jointly follow a multivariate normal distribution. The general model was based on 4 groups of individuals (ie, fathers, f, mothers, m, sons, s, and daughters, d, giving rise to 8 correlations in 3 familial classes: 1 spouse (fm), 4 parent-offspring (fs, fd, ms, and md), and 3 sibling (ss, dd, and sd). Specific null hypotheses were also evaluated. Each null hypothesis was tested by comparing it with the general model using the likelihood ratio test (LRT), which is the difference in minus twice the log-likelihood (−2 ln L) obtained under two nested models. The likelihood ratio is approximately distributed as a χ^2 with the degrees of freedom (*df*) being equal to the difference in the number of parameters estimated in the two models. In addition to the LRT, Akaike's Information Criterion (AIC), which is −2 ln L plus twice the number of estimated parameters, was used to compare non-nested models. The "best" model is the one with the smallest AIC.[17]

Two general series of null hypotheses were tested (Table 2). Sex and generation differences were tested in the first series, and in the second series we examined the significance of various correlations. In addition, a single correlation model was fit to the data by equating all 8

Table 2. Familial Correlation Model-Fitting Summary

Model	*df*	χ^2	*P*	AIC
Baseline DHEAS				
1) fm, fs, fd, ms, md, ss, sd, dd	0	—	—	1,331.97
2) fs = fd, ms = md, ss = dd = sd	4	12.74	.01*	1,336.71
3) fs = fd = ms = md, ss = dd = sd	5	12.99	.02*	1,334.96
4) fs = fd = ms = md = ss = dd = sd	6	13.85	.03*	1,333.82
5) ss = sd = dd = 0	3	48.31	<.01*	1,374.28
6) fs = fd = ms = md = 0	4	31.01	<.01*	1,354.98
7) fm = 0	1	5.49	.02*	1,335.46
8) fm = fs = fd = ms = md = ss = sd = dd	7	13.86	.05*	1,331.83
9) fm = fs = fd = ms = md = ss = sd = dd = 0	8	81.17	<.01*	1,397.14
Parsimonious				
1) fm, fs, fd, ms, md, ss, sd, dd	0	—	—	1,331.97
DHEAS response to training				
1) fm, fs, fd, ms, md, ss, sd, dd	0	—	—	1,409.50
2) fs = fd, ms = md, ss = dd = sd	4	4.54	.34	1,406.04
3) fs = fd = ms = md, ss = dd = sd	5	5.00	.42	1,404.50
4) fs = fd = ms = md = ss = dd = sd	6	5.05	.54	1,402.55
5) ss = sd = dd = 0	3	4.53	.21	1,408.03
6) fs = fd = ms = md = 0	4	10.51	.03*	1,412.01
7) fm = 0	1	2.19	.14	1,409.69
8) fm = fs = fd = ms = md = ss = sd = dd	7	5.18	.64	1,400.68
9) fm = fs = fd = ms = md = ss = sd = dd = 0	8	18.13	.02*	1,411.63
Parsimonious				
10) fm = ss = sd = dd = 0, fs = fd = ms = md	7	12.32	.09	1,407.82
8) fm = fs = fd = ms = md = ss = sd = dd	7	5.18	.64	1,400.68
DHEAS response to training in the subset of 56 responsive families				
1) fm, fs, fd, ms, md, ss, sd, dd	0	—	—	888.59
2) fs = fd, ms = md, ss = dd = sd	4	4.19	.38	886.78
3) fs = fd = ms = md, ss = dd = sd	5	4.25	.51	884.84
4) fs = fd = ms = md = ss = dd = sd	6	4.32	.63	882.91
5) ss = sd = dd = 0	3	2.85	.42	887.44
6) fs = fd = ms = md = 0	4	9.14	.06	891.73
7) fm = 0	1	2.84	.09	891.43
8) fm = fs = fd = ms = md = ss = sd = dd	7	4.76	.69	881.35
9) fm = fs = fd = ms = md = ss = sd = dd = 0	8	14.84	.06	889.43
Parsimonious				
8) fm = fs = fd = ms = md = ss = sd = dd	7	4.76	.69	881.35

*$P < .05$.

correlations. Finally, a non–familial correlation hypothesis was also assessed. A parsimonious model was derived by combining the nonrejected hypotheses into a single test. Maximal heritability was computed using the familial correlations from the most parsimonious model (see Table 3 for equation).[18] This estimate includes both polygenic and familial environmental sources of variance and is adjusted for the degree of spouse resemblance.

Commingling Analysis

The method of commingling analysis as described in MacLean et al[19] and implemented in the computer program SKUMIX[20] was used. A mixture of up to 3 distributions in Hardy-Weinberg proportions can be fitted optionally including *p*, a Box-Cox power transformation parameter. There are 5 additional parameters in the model: the common variance in each component (E), the overall mean (u), the relative proportion (q^2) of the component distribution with the highest mean (q), the displacement between the two extreme component means (t), and the relative position of the mean of the middle component (d). These parameters were estimated by the maximum likelihood method. Hypothesis tests for nested models were performed using the LRT, and non-nested models were compared using the AIC.

Segregation Analysis

As implemented in the computer program POINTER,[19-21] segregation analysis was performed using the unified mixed model.[22] This model assumes that a phenotype is composed of the independent and additive contributions from a major effect, a heritable multifactorial background, and a unique environmental residual. The major effect is assumed to result from the segregation at a single locus with two alleles (A and a). The a allele is defined to be associated with higher trait values. Included in the model are 7 parameters: the overall variance (V), the overall mean (u), the frequency of the a allele (q), the displacement between the two homozygous means (t), the relative position of the heterozygous mean or dominance (d), and the multifactorial heritability in offspring (H) and in parents (HZ). We note that u, q, t, and d are parameterized identically to those in SKUMIX. The transmission pattern of the major gene from parents to offspring is characterized by 3 parameters: τ_1 is the probability that an AA individual transmits allele A to the offspring, τ_2 is the probability that Aa transmits A, and τ_3 is the probability that aa transmits A. Under Mendelian transmission, $\tau_1 = 1$, $\tau_2 = 0.5$, and $\tau_3 = 0$. When the three τ values are equal, no transmission of the major effect is obtained. The following three conditions are usually required to infer a major gene[21]: (1) rejection of the no-major-effect hypothesis ($q = t = d = 0$), (2) nonrejection of the Mendelian transmission hypothesis (Mendelian τs), and (3) rejection of the no-transmission hypothesis (equal τs). Competing models are tested for significance using the LRT.

RESULTS

The reproducibility of pretraining DHEAS measures was very high, with intraclass correlations for repeated measures of .96 and .97 in 325 males and 420 females, respectively, in the present study. The coefficient of variation for repeated measures was 16% and 18% in these males and females, respectively, in the HERITAGE Family Study. The mean baseline DHEAS and DHEAS response to training are listed in Table 1. Based on a comparison of standard errors (SEs), there were significant generation and sex differences in the mean baseline DHEAS, with higher levels in parents versus offspring within sex and higher levels in males versus females within generation. There were no significant sex and generation differences for the mean change in DHEAS in response to training, based on a SE comparison.

For baseline DHEAS, age^2 accounted for 13.3% of the variance in fathers and age accounted for 9.8% and 4.4% of the variance in mothers and daughters, respectively. The BMI was not a significant predictor of baseline DHEAS. Baseline DHEAS accounted for 5.9% and 16.5% of the variance in the response to

training in sons and daughters, respectively. In the subset of 56 "responsive" families, baseline DHEAS accounted for 13.8% and 24.0% of the variance in the response to training in sons and daughters, respectively.

Familial correlation model-fitting results are listed in Table 2. For baseline DHEAS, P values for all of the competing models (models 2 to 9) were significant, suggesting the presence of parent-offspring, sibling, and spouse resemblance with full sex and generation differences. According to the LRT, the general hypothesis (model 1, AIC = 1,331.97) provided the most parsimonious fit, although the single correlation hypothesis also provided a reasonable fit (model 8, $\chi^2 = 13.86$, $P = .05$, AIC = 1,331.83). For the DHEAS response to training, none of the models testing sex and generation differences were rejected (models 2 to 4). The sibling (model 5) and spouse (model 7) correlations were not significant, but the parent-offspring correlations (model 6, $\chi^2 = 10.51$, $P = .03$) were significant. The hypothesis of no familial correlations (model 9) was rejected ($\chi^2 = 18.13$, $P = .02$), while the single correlation hypothesis (model 8) was not rejected. Although the combined test of no sibling or spouse correlations and no sex differences in the parent-offspring correlations (model 10) was not rejected by the LRT ($\chi^2 = 12.32$, $P = .09$, AIC = 1,407.82), the AIC suggested that the single correlation hypothesis (model 8, AIC = 1,400.68) was the most parsimonious. For the DHEAS response to training in the subset of 56 responsive families, P values for all of the competing models (models 2 to 9) were nonsignificant. Although the test for no familial resemblance was not rejected ($\chi^2 = 14.84$, $P = .06$, AIC = 889.43), the single correlation hypothesis (model 8, AIC = 881.35) provided the "best" fit. Parameter estimates (correlation ± SE) are listed in Table 3 under both the general and the most parsimonious models for baseline DHEAS and the DHEAS response to training. The maximal heritability estimates, which include both genetic and familial environmental sources of variance, were 58% for baseline DHEAS, 26% for the DHEAS response to training in the complete sample, and 30% for the DHEAS response to training in the subset of 56 responsive families.

The commingling analysis suggested that the best models consist of mixtures of three normal distributions for age-adjusted baseline DHEAS and the age-baseline–adjusted DHEAS response to training in the complete sample, while two normal distributions best fit the age-baseline–adjusted DHEAS response to training in the subset of 56 responsive families (Fig 1). The parameter estimates for each commingling model are shown in the figure. The finding of commingled distributions is compatible with a major gene hypothesis; however, commingling may also arise for other reasons. Thus, segregation analysis was used to determine if these major effects segregated in families according to Mendelian expectations.

Segregation analysis results are summarized in Table 4 for baseline DHEAS and the DHEAS response to training. The parameter estimates under the most parsimonious segregation models are listed in Table 5. For age-adjusted baseline DHEAS (Table 4), the hypotheses of no multifactorial effect (model 2, $\chi^2_2 = 0$, $P = .99$) and no major effect (model 3, $\chi^2_3 = 0$, $P = .07$) were not rejected, while the hypothesis of no familial effect (model 4, $\chi^2_5 = 67.33$, $P < .01$) was rejected. This pattern would suggest the presence of the familiality, which was nondifferentiable between the multifactorial effect and the

Table 3. Familial Correlations and Heritability Estimates

Parameters	Baseline (complete sample)	Response to training: Complete Sample	Response to training: Subset of 56 Families
General model			
fm	0.27 ± 0.10	0.16 ± 0.10	0.23 ± 0.13
fs	0.34 ± 0.08	0.01 ± 0.10	0.04 ± 0.12
fd	0.21 ± 0.08	0.17 ± 0.08	0.25 ± 0.10
ms	0.24 ± 0.09	0.07 ± 0.10	0.11 ± 0.12
md	0.38 ± 0.07	0.24 ± 0.08	0.25 ± 0.10
ss	0.40 ± 0.10	0.19 ± 0.11	0.16 ± 0.13
sd	0.47 ± 0.12	0.10 ± 0.10	0.11 ± 0.13
dd	0.20 ± 0.09	0.04 ± 0.12	−0.02 ± 0.14
Parsimonious model			
fm	0.27 ± 0.10	0.13 ± 0.04	0.15 ± 0.06
fs	0.34 ± 0.08	[0.13]	[0.15]
fd	0.21 ± 0.08	[0.13]	[0.15]
ms	0.24 ± 0.09	[0.13]	[0.15]
md	0.38 ± 0.07	[0.13]	[0.15]
ss	0.40 ± 0.10	[0.13]	[0.15]
sd	0.47 ± 0.12	[0.13]	[0.15]
dd	0.20 ± 0.09	[0.13]	[0.15]
Maximal heritability	58% ± 18%	26% ± 8%	30% ± 12%

NOTE. Maximal heritability is computed as $[(r_{sibling} + r_{parent\text{-}offspring})(1 + r_{spouse})/(1 + r_{spouse} + 2 \cdot r_{spouse} \cdot r_{parent\text{-}offspring})]$, including both genetic and familial environmental sources of variance, and is adjusted for the degree of spouse resemblance. Values in brackets were equated to a preceding value.

major gene effect. Further, the hypothesis of no generation difference in the multifactorial effect in the absence of the major gene effect was not rejected (model 5, $\chi^2_4 = 8.93$, $P = .06$). In the absence of the multifactorial effect, both the recessive (model 6, $\chi^2_3 = 16.08$, $P < .01$) and dominant (model 8, $\chi^2_3 = 12.30$, $P < .01$) modes of transmission were rejected, while the additive (model 7, $\chi^2_3 = 3.39$, $P = .34$) mode fit the data. Tests of the transmission probabilities were performed under the parsimonious Mendelian hypothesis (model 7, an additive major gene with no multifactorial component). Mendelian τs were not rejected (model 7 to model 9, $\chi^2_3 = 0.66$, $P = .88$), while the constrained-equal-τs ($\tau_1 = \tau_2 = \tau_3 = 1 - q$) hypothesis was rejected (model 10 to model 9, $\chi^2_3 = 64.60$, $P < .01$). In summary, the evidence suggests an additive major gene which accounts for 50% of the overall phenotypic variance, and an estimated 46% (q^2) of the sample may carry the homozygous *aa* genotype.

For the age-baseline–adjusted DHEAS response to training, the hypotheses of no major effect and no familial effect were rejected, while the hypothesis of no multifactorial component was not rejected. Additive and dominant modes of inheritance were rejected, while the recessive mode was not rejected. Transmission probability tests were performed under the parsimonious Mendelian hypothesis (model 5, a recessive major locus with no multifactorial component). Although the Mendelian τs were not rejected (model 5 to model 8, $\chi^2_3 = 4.18$, $P = .24$), the equal-τs hypothesis also was not rejected (model 9 to model 8, $\chi^2_3 = 4.65$, $P = .20$). Since neither the equal-τs nor the Mendelian-τs models were rejected, the AIC was used to determine which model best fit the data. The recessive Mendelian model (model 5, AIC = 837.28) appears to provide a nominally better fit than the equal-τs model (AIC = 837.75). The major effect accounted for 38% of the overall phenotypic

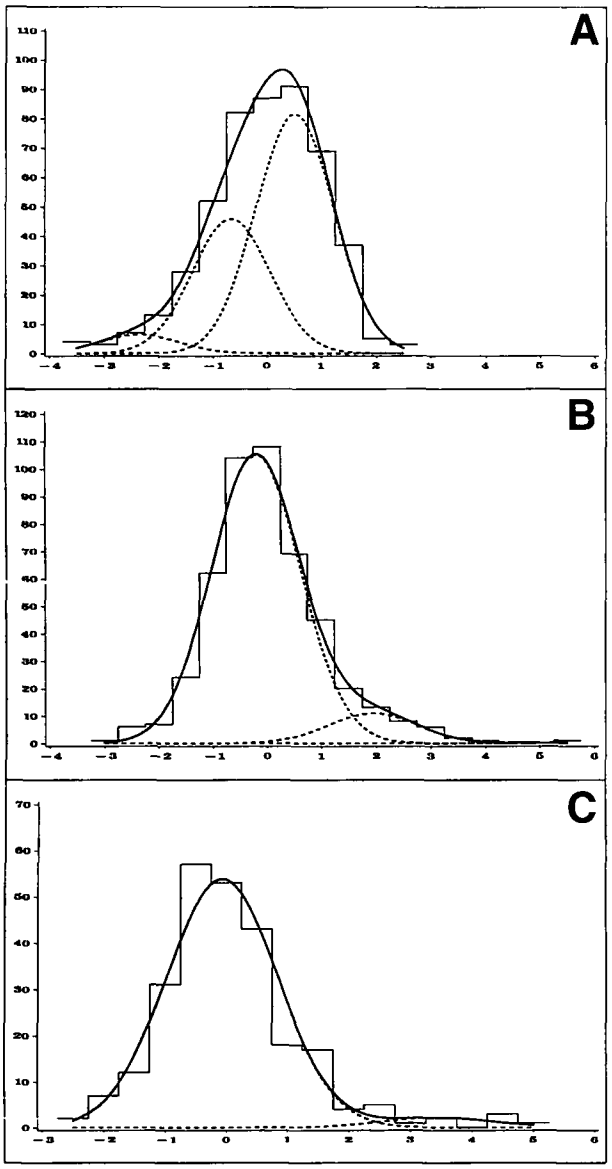

Fig 1. (A) Histogram of age-adjusted baseline DHEAS with the most parsimonious commingling model (3 normal distributions) superimposed: E = 0.51284, u = −0.02858, d = 0.58971, t = 2.85614, q = 0.78029, *P* = .99. (----) Component distributions; (—) overall distribution. Horizontal axis represents age-adjusted baseline DHEAS, and vertical axis denotes the number of individuals. (B) Histogram of the age-baseline–adjusted DHEAS response to training with the most parsimonious commingling model (3 normal distributions) superimposed: E = 0.66738, u = 0.01341, d = 0.42790, t = 5.02729, q = 0.04922, *P* = .99. (C) Histogram of the age-baseline–adjusted DHEAS response to training in the subset of 56 responsive families with the most parsimonious commingling model (2 normal distributions) superimposed: E = 0.82964, u = 0.07266, d = 0, t = 3.53343, q = 0.19852, *P* = .99.

variance in the DHEAS response to training, and 6% of the sample are homozygous recessive (*aa*).

For the age-baseline–adjusted DHEAS response to training in the subset of 56 responsive families, the hypotheses of no major effect and no familial effects were rejected, while the hypothesis of no multifactorial effect was not rejected. None of the recessive, additive, and dominant hypotheses were rejected; therefore, transmission probability tests were performed under the parsimonious Mendelian hypothesis (model 2, no multifactorial effect and no constraints on the mode of inheritance). While the Mendelian τs were not rejected (model 2 to model 10, $\chi^2_2 = 0.58$, $P = .75$), the equal-τs hypothesis was rejected (model 11 to model 10, $\chi^2_2 = 12.87$, $P < .01$). A Mendelian major gene with an undetermined ($d = 0.19$) mode of inheritance was inferred which accounted for 33% of the overall

Table 4. Segregation Analysis of DHEAS

Model	*df*	−2 ln L	χ^2	*P*	AIC
Baseline DHEAS					
1. General Mendelian	0	800.25	—	—	814.25
2. No multifactorial (H = Z = 0)	2	800.25	0.00	.99	810.25
3. No major effect (d = t = q = 0)	3	807.25	7.00	.07	815.25
4. No familial (d = t = q = H = Z = 0)	5	867.58	67.33	<.01*	871.58
5. No generation difference (d = t = q = 0, Z = 1)	4	809.18	8.93	.06	815.18
6. Recessive (d = 0, H = Z = 0)	3	816.33	16.08	<.01*	824.33
7. Additive (d = 0.5, H = Z = 0)	3	803.64	3.39	.34	811.64
8. Dominant (d = 1, H = Z = 0)	3	812.55	12.30	<.01*	820.55
9. Free τs (d = 0.5, H = Z = 0)	3	802.98	0.66	.88	816.98
10. Equal τs (1 − q; d = 0.5, H = Z = 0)	3	867.58	64.60	<.01*	875.58
DHEAS response to training					
In the complete sample					
1. General Mendelian	0	823.77	—	—	837.77
2. No multifactorial (H = Z = 0)	2	827.49	3.72	.16	837.49
3. No major effect (d = t = q = 0)	3	854.45	30.68	<.01*	862.45
4. No familial (d = t = q = H = Z = 0)	5	865.27	41.50	<.01*	869.27
5. Recessive (d = 0, H = Z = 0)	3	829.28	5.51	.14	837.28
6. Additive (d = 0.5, H = Z = 0)	3	840.92	17.15	<.01*	848.92
7. Dominant (d = 1, H = Z = 0)	3	841.56	17.79	<.01*	849.56
8. Free τs (d = 0, H = Z = 0)	3	825.10	4.18	.24	839.10
9. Equal τs (1 − q; d = 0, H = Z = 0)	3	829.75	4.65	.20	837.75
In the subset of 56 families					
1. General Mendelian	0	437.20	—	—	451.20
2. No multifactorial (H = Z = 0)	2	437.65	0.45	.80	447.65
3. No major effect (d = t = q = 0)	3	456.51	19.31	<.01*	464.51
4. No familial (d = t = q = H = Z = 0)	5	471.72	34.52	<.01*	479.72
5. Recessive (d = 0, H = Z = 0)	3	442.34	5.14	.16	450.34
6. Additive (d = 0.5, H = Z = 0)	3	443.63	6.43	.09	451.63
7. Dominant (d = 1, H = Z = 0)	3	443.57	6.37	.09	451.57
8. Free τs (H = Z = 0)	2	437.07	0.58	.75	453.07
9. Equal τs (1 − q; H = Z = 0)	3	449.94	12.87	<.01*	457.94

*$P < .05$.

Table 5. Parsimonious Segregation Models for DHEAS ($H = Z = 0$)

DHEAS	V	u	d	t	q	%*	q^2
Baseline†	1.06 ± 0.06	−0.06 ± 0.08	[0.5]	2.19 ± 0.13	0.68 ± 0.05	50%	46%
Response‡	1.16 ± 0.11	0.03 ± 0.05	[0]	2.70 ± 0.19	0.25 ± 0.03	38%	6%
Response§	1.06 ± 0.14	−0.01 ± 0.08	0.19 ± 0.04	3.59 ± 0.39	0.15 ± 0.04	33%	2%

*Percentage accounted for by major effects.

†Mendelian transmission for age-adjusted baseline DHEAS.

‡Mendelian transmission for the age-baseline–adjusted DHEAS response to training.

§Mendelian transmission for the age-baseline–adjusted DHEAS response to training in the subset of 56 responsive families.

phenotypic variance, and an estimated 2% of the sample carried the homozygous *aa* genotype.

DISCUSSION

This investigation was undertaken to provide heritability estimates and to assess a major gene hypothesis for baseline serum DHEAS levels in sedentary Caucasian families, as well as changes in DHEAS levels in response to a 20-week endurance exercise training program. Since the physical activity level, a potentially important environmental correlate, was controlled for at baseline, it is interesting to compare heritability estimates from these physically inactive families at baseline with findings from other heterogeneous samples, which presumably include a mixture of active and inactive families. In addition, this is the first study to investigate a major gene hypothesis for DHEAS levels, which could provide a better understanding of the etiology of DHEAS determinations.

In this study, baseline DHEAS concentrations, as expected, were not normally distributed, and thus were log-transformed prior to regression and genetic analysis. Previously, both log transforms[7] and square-root transforms[8-10] were used. The maximal heritability estimate found for baseline DHEAS in this study (58%) is the same as that (58%) reported by Meikle et al[9] and within the range reported by other investigators, from 45% to 65%.[7,10] However, our estimate is higher than the 39% reported by Jaquish et al,[8] which was attributed to polygenic factors alone (narrow sense heritability). Jaquish et al[8] also suggested that sex affected the mean DHEAS levels, but not the genetic variance. Nevertheless, the maximal heritability estimates are somewhat higher in males (65%) than in females (50%) in the current study, while Rice et al[7] reported an opposite pattern of higher estimates in females (74%) versus males (29%). Finally, there are no data on the heritability for the DHEAS response to training. Our heritability estimate of 30% for this phenotype provides new information.

In the current study, the notable spouse correlations (27% for baseline DHEAS) may be largely explained by common environmental factors. The BMI was not a significant predictor of DHEAS levels in the current study. Therefore, assortative mating for relative weight did not contribute to the high spouse resemblance in DHEAS levels.

Segregation analysis suggests that baseline DHEAS is influenced by an additive Mendelian locus which accounts for 50% of the phenotypic variance. An estimated 46% (q^2) of the sample are homozygous for the *aa* genotype (leading to higher DHEAS levels). It is interesting to note that no residual multifactorial component was found. Further findings from the present study provide evidence for a major gene controlling the DHEAS response to training. In the complete sample, the major effect exhibited ambiguous (Mendelian or environmental) transmission from parents to offspring. However, the transmission probabilities were clearly Mendelian in the subset of 56 responsive families. This subset may be potentially more homogeneous in terms of DHEAS responsiveness to training, providing better power for detection of the major locus. Although the mode of inheritance was not differentiable ($d = 0.19$), the locus accounted for 33% of the overall phenotypic variance. An estimated 2% of the sample are homozygous for the *aa* genotype.

Major gene effects were revealed for baseline DHEAS as well as the response to training in the present study, and it is possible that these are two different loci. First, we note that these two phenotypes are very different, since the effect of baseline DHEAS was removed from the response to training. Second, we note that the parameters of the two loci are very different. For baseline DHEAS, we found an additive locus, with the less frequent allele leading to low DHEAS values (Fig 1A). For the response to training, the mode of inheritance is nearly recessive, with the less frequent allele giving rise to high values (Fig 1B and C). If the same gene influenced both variables, then we would have expected the major gene effect for the response to training to be attenuated. Whether there is a single pleiotropic and/or two separate genes controlling baseline DHEAS levels and the response to training should be examined by performing a bivariate segregation analysis.

Another interesting finding in this study is that the familial effect is apparently entirely due to the major effect and not to multifactorial factors. The percentage of variance accounted for solely by the additive locus for baseline DHEAS (50%) is similar to that accounted for by the multifactorial effects using the correlation method in the current study (58%) and in other studies reviewed earlier that did not consider a major gene model. This finding is consistent since the putative locus noted here is additive in nature.

In conclusion, the maximal heritability estimates were 58% and 26% for baseline serum DHEAS and the DHEAS response to training, respectively, in a sample of 99 Caucasian families of the HERITAGE Family Study. Our heritability estimate for baseline DHEAS is generally in accordance with previous findings, suggesting that the magnitude of the familial effect in these sedentary families is similar to that in the general population. The segregation analysis further suggests that this effect is more likely due to an additive major gene rather than multifactorial effects. In addition, a major gene effect was found in the subset of 56 responsive families for the DHEAS response to training, although in the complete sample (99 families) the major locus evidence was less compelling. The present investigation represents the first study to report the presence of a

significant heritability for the DHEAS response to training, and to report a Mendelian major gene or genes influencing baseline DHEAS levels and the DHEAS response to training. This finding may provide a basis to search for candidate gene(s) in the immediate future. Genome-wide linkage scans and association studies may be used to locate the gene(s) regulating baseline DHEAS and the response to training.

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